origin.

Please cancel claims 27-29 without prejudice.

REMARKS

The amendments to the claims are supported by claims 1-14 as filed and the specification at pages 3-5. The amendments are made to more particularly point out and specifically claim a preferred embodiment of what applicants regard as the present invention.

Claims 15-30 were pending. However, because claim 11 was inadvertently numbered claim 12 in the Preliminary Amendment filed on May 5, 1997, the Examiner renumbered claims 15-30 as claims 14-29, so claims 14-29 were pending. With the cancellation of claims 27-29, claims 14-26 are pending.

Information Disclosure Statement

The response filed September 30, 1998 requests that the Examiner acknowledged the consideration of the Information Disclosure Statement filed on May 5, 1997, but the Final Office Action does not indicate whether the Information Disclosure Statement was considered by the Examiner. The Examiner is requested again to consider the Information Disclosure Statement and send applicant a copy with his initials.

Claim Rejections – 35 U.S.C. 112, First Paragraph

Claims 14-29 were rejected because the Final Office Action asserts that the disclosure fails to adequately teach how to use the claimed methods based on two reasons. Applicant respectfully traverses the rejection.

I. Fragments, Derivatives and Mutants of EPO

The Office Action asserts that one skilled in the art would not be able to identify, without undue experimentation, EPO fragments without the specification disclosing the desired functional activity and disclosing the conserved structure. The Office Action states that the artisan would have to determine all the known and unknown functional activities of EPO and then to determine which compounds had similar activities. Applicant respectfully disagrees that the specification fails to disclose the desired functional activity and the artisan would have to determine all the known and unknown functional activities of EPO. This is because page 3, the fourth paragraph, discloses that any EPO derivatives, mutants or fragments thereof that (1) are nonimmunogenic upon administration and (2) have an ameliorating effect on chronic inflammation would be effective in the claimed methods. Therefore, the artisan is required to determine only one functional activity of EPO, i.e. amelioration of chronic inflammation, which can be determined with a reasonable amount of experimentation. Applicant notes that only a reasonable amount of experimentation would be required for the artisan to determine whether a compound is a EPO derivative, mutant or fragment that works in the claimed method (by looking for only two biological properties: (1) being nonimmunogenic upon

administration and (2) having an ameliorating effect on chronic inflammation).

The Office Action asserts that the specification does not disclose the conserved structure and the Office Action cites the paper by Smilek that even minor change in the structure of a biologically active molecule can have drastic effects on function activity. Applicant respectfully disagrees. Smilek's paper is not relevant because Smilek deals with only a myelin basic protein which is very different from EPO both functionally and structurally.

Although the instant claims are fully enabled, in order to advance prosecution, applicant deletes "an erythropoietin derivative, erythropoietin mutant or fragments thereof" from claims 14, 18, 20, 22, 24 and 26 and also cancels claims 27-29. Withdrawal of the nonenablement rejection is requested.

II. Autoimmune Disease, Scope

Claims 14-29 were rejected because the Final Office Action asserts that the specification fails to teach one skilled in the art how to use the claimed methods to treat diseases other than rheumatoid arthritis using EPO due to the complexity of the physiological mechanisms of different antoimmune diseases. Applicant respectfully traverses the rejection.

First, claims 17-20 and 23-26 are directed to the treatment of the chronic inflammation, symptoms or a disease activity of rheumatoid arthrities. Since the Final Office Action already states that EPO is effective in treating rheumatoid arthritis, the nonenablement rejection of claims 17-20 and 23-26 should be withdrawn now that "an

erythropoietin derivative, erythropoietin mutant or fragments thereof" is deleted from these claims.

Second, the Final Office Action makes an erroneous characterization of the methods claimed. Claims 14-16, 21 and 22 are directed to methods of treating chronic inflammation, which inflammation could be associated with an immune disease or auto-immune disease (and claims 17-20 and 23-26 are directed to chronic inflammation, symptoms or a disease activity of rheumatoid arthritis as discussed above). However, the Final Office Action erroneously assumes claims 14-17, 22 and 23 to be directed to a method of treating immune diseases or auto-immune diseases, but actually the methods of claims 14-17, 22 and 23 are for treating chronic inflammation. The Final Office Action already admits that EPO affects the cytokine levels. Pages 4 and 5 of the specification disclose that EPO induces a T_{h2} cytokine secretion profile. It is well known that cytokines play an important role in mediating the chronic inflammatory response. Page 5 of the specification discloses that EPO counteracts the activity of tumor necrosis factor-alpha, which is an important pro-inflammatory cytokines and EPO reduces the production of neutrophils, which are important in inflammation. Working examples also demonstrate that EPO is effective in treating chronic inflammatory symptoms of rheumatoid arthritis. Therefore, there is sufficient teachings in the specification that the claimed methods are effective in treating chronic inflammation, especially chronic inflammatory symptoms in immune diseases or auto-immune diseases, and to practice the claimed methods would not involve an unreasonable amount of experimentation based on the disclosure and what one skilled in the art

already knows. Withdrawal of the nonenablement rejection is respectfully requested.

Claim Rejection – 35 U.S.C. 102(b)

Claims 14-29 were rejected as anticipated by GB 2 171 304 because GB '304 teaches using EPO to treat anemia of rheumatoid arthritis and performance of the method of GB '304 would inherently treat symptoms, such as joint swelling, pain or inflammation of rheumatoid arthritis. Applicant respectfully traverses the rejection.

GB '304 teaches a method of treating anemia of rheumatoid arthritis by administering human EPO (see page 1, lines 5-7). GB '304 does not teach or suggest using EPO to treat chronic inflammation or to treat morning stiffness, painful and swollen joints, pain, and a loss of grip strength in rheumatoid arthritis. GB '304 does not teach every limitation of the claims, so there is no anticipation of the claims.

There is a significant difference between the method taught by GB '304 and the methods claimed in the instant application in terms of the EPO administration period. Page 2, lines 23-27, of GB '304 discloses that the EPO dosage and frequency of administration may be determined depending on the patient's condition, but ordinarily 0.1-500 μg of EPO may be administered to an adult in 1 to 7 doses for one week, assuming a human EPO activity of 9×10^4 units per mg EPO. Because the average body weight of a human adult is 70 kg, that means GB '304 teaches administering 1.3×10^2 to 6.4×10^5 units of EPO per kg body weight in 1 to 7 doses **for one week**. Page 6, lines 16-19, of the instant specification teaches administering 240 units of EPO per kg body weight subcutaneously 3 times a week **for 6 weeks**. Our dose of 240 units/kg is

embraced by the prior art's 1.3×10^2 to 6.4×10^5 units/kg, but we can emphasize the difference in the period of EPO treatment. Page 3, lines 11-12, of the instant specification also discloses that EPO treatments resulted in a significant improvement of chronic inflammation and clinical variables, such as joint pain, **after 2 weeks** of EPO treatment. Tables III-V show that it takes 3-6 weeks of EPO administration to treat chronic inflammation and certain signs or symptoms of rheumatoid arthritis. Thus, the methods of the present invention require EPO treatment of **at least 2 weeks**, while GB '304 teaches administering EPO **for only one week**. Therefore, GB '304 fails to anticipate claims 14-29 because GB '304 does not teach the period of EPO treatment required in the claimed methods.

Applicant submits that claims 14-29 with the "at least 2 weeks" limitation is also not obvious over GB '304. There is no motivation or suggestion in the prior art to at least double the treatment period of GB '304 to arrive at the claimed methods. Applicant notes that page 3, lines 11-12, of the instant specification already teaches that administering EPO for a period of "at least 2 weeks" is critical to the treatment of chronic inflammation and pain, etc., in rheumatoid arthritis. There would have been no suggestion in the prior art to administer EPO for more than 1 week to treat the diseases as in the claimed method.

Conclusion

With the above amendments and reasoning, applicant respectfully requests that all rejections be withdrawn. Applicant submits that the application is in a condition for

allowance.

In case this paper is not timely filed, the undersigned hereby petitions for an appropriate extension of time. In the event that any fees are due in connection with this paper, please charge our Deposit Account No. 14-1060.

Respectfully submitted,
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